Biomedical Science

Cancer Genes

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Cancer is a genetic disease; tumor cells differ from their normal progenitors by genetic alterations that affect growth-regulatory genes. There exist 2 classes of such cancer genes: the oncogenes, which function as positive growth regulators, and the tumor suppressor genes, which function as negative growth regulators. Oncogenes are widely conserved among diverse forms of life and are active in transmitting growth signals from the cell periphery to the cell nucleus. These signaling functions can be disturbed by many types of genetic change; the result of an altered growth signal is often cancer. Tumor suppressor genes have an attenuating effect on cell growth that is lost as a result of inactivating mutations or deletion of the gene; in DNA virus–transformed cells, it is abrogated by neutralization of the tumor suppressor protein through a viral gene product. Tumor suppressor genes were first recognized in inherited cancers; defects in a tumor suppressor transmitted through the germ line can lead to increased tumor incidence in the offspring. Tumor suppressors also play important roles in nonheritable cancer, however; many tumors in humans show defects in tumor suppressor genes.

Most cancers harbor multiple genetic changes in oncogenes as well as tumor suppressor genes. Oncogenes induce aberrant growth through a gain in function; tumor suppressor genes contribute to oncogenesis through a loss of function. Both types of mutation work together to produce cancer; the changes are not constant but increase in number as the tumor develops from benign to more and more malignant. Cancer results from the accumulation of genetic changes. Oncogenes and tumor suppressor genes provide important insights into the regulation of cell growth. This knowledge can now be used to develop gene-specific therapies for cancer.

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Research in the past 30 years has led to a convergence of ideas about cancer. By almost universal consensus, cancer is now viewed as resulting from changes in a few key regulatory genes. The disciplines of cancer research have also converged to focus on genes that regulate cell growth and differentiation. The major impulses for this remarkable development have come from virology. Viruses have been the tools of discovery for cancer genes, and virology has played a major role in transforming cancer research into a genetic science.

Two kinds of cellular genes are altered in cancer: positive growth regulators, called oncogenes, and negative regulators, referred to as tumor suppressor genes. The existence of cellular oncogenes was revealed through the study of retroviruses. Our understanding of tumor suppressor genes has been greatly advanced by their interactions with DNA tumor viruses. In this article I summarize the new molecular genetics of cancer and trace its origins back to the seminal work of two great pioneers, Peyton Rous and Theodor Boveri.

Retroviral Oncogenes

Retroviruses are RNA viruses that replicate by a unique mechanism: Their RNA genome is transcribed into DNA and inserted into the chromosomal DNA of the cell. The integrated provirus is then transcribed into viral messenger RNA and into progeny RNA genomes. Viral proteins made in the cytoplasm are assembled into viral particles that bud from the plasma membrane. As a rule, retroviruses do not kill the host cell but allow it to survive and may even transform it into a tumor cell.

The discovery of oncogenes was triggered by the simple observation that there are two kinds of retroviruses, those that transform cells in culture and induce tumors rapidly and those that do not transform cultured cells and are tumorigenic only after a long latent period. An exemplary pair of these two kinds of retroviruses is Rous sarcoma virus (RSV), which turns cultured chicken fibroblasts into tumor cells, and its close relative transformation-defective RSV (*td*RSV), which has lost this transforming potential for cells in culture. Both viruses are infectious and can multiply in chicken cells. The retrovirus RSV, however, contains an additional gene not needed for virus survival but required for tumorigenesis. This extra gene, the *src* oncogene, is absent from *td*RSV. Otherwise the genetic material of *td*RSV is identical to that of RSV and contains all information needed to direct the synthesis of retroviral progeny.

This simple difference between RSV and *td*RSV can be used to isolate DNA that is specific for the oncogene (Figure 1). In this isolation procedure, the RNA genome of RSV is transcribed enzymatically in the test tube into a single-stranded complementary DNA copy. The copied material is then allowed to bind to the RNA from *td*RSV. All complementary DNA will anneal to form a double-stranded DNA-RNA complex. The DNA of the *src* oncogene, however, has

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ABBREVIATIONS USED IN TEXT

Rb = retinoblastoma viral protein
RSV = Rous sarcoma virus
SV40 = simian virus 40
*td*RSV = transformation-defective RSV

no counterpart in the RNA of *td*RSV, and it remains single stranded in this reaction. The single-stranded nucleic acid can be separated from the double-stranded forms; the result is a DNA probe for the *src* oncogene. This complementary probe binds to nucleic acids having the same sequence information as *src* and, properly labeled, can therefore detect the *src* oncogene in any genetic material.

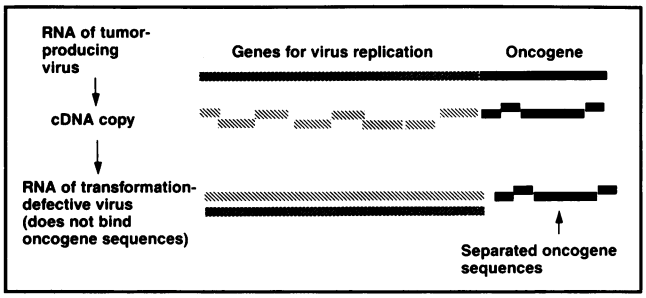

Figure 1.—The RNA genome of Rous sarcoma virus (RSV), a tumor-inducing retrovirus, is transcribed into complementary DNA representing the whole genome but consisting of numerous small pieces. The DNA is then allowed to anneal by base pairing to the RNA genome of *td*RSV, a nontransforming virus that lacks the *src* oncogene. All DNA will bind to RNA except those fragments containing *src* information. This single-stranded, complementary *src* DNA can be separated from the double-stranded RNA-DNA hybrid molecules.

A search with the *src* probe revealed the surprising fact that *src*, although carried by a virus, is originally a cellular gene. It is not only present in the cells of chickens, which are the natural hosts for RSV, but is conserved in the cells of all vertebrates. Similar probes have established a host origin for all other retroviral oncogenes. They are cellular, not viral, genes, accidentally incorporated into the viral genome and then transduced by the virus from cell to cell.

TABLE 1.—*Functional Classes of Retroviral Oncogenes*

Function	*Oncogene*
Growth factor	*sis*
Receptor tyrosine kinase	*erb* B
	fms
	ros
	sea
Signal protein	*ras*
Nonreceptor tyrosine kinase	*src*
	yes
	fps
	abl
Serine threonine kinase	*raf*
	mos
Cytoplasmic regulator	*crk*
Transcription factor	*jun*
	fos
	erb A
	rel
	ski
	myc
	myb

Oncogenes Function in Cellular Signal Transduction

The growth and division of cells is governed by external signals. These may be peptide growth factors or hormones that bind to and activate specific cellular receptors. Activated receptors then propagate the signal, either directly or through a series of sequential protein-protein interactions to the cell nucleus. In the nucleus, the signals are converted into programmed responses of the cell, consisting of specific patterns of gene expression. Most retroviral oncogenes code for protein components of the signal transduction chains that guide the signal from the cell periphery to its interaction with the cell genome (Table 1). Oncogenes code for growth factors, growth factor or hormone receptors, signal-transducing proteins, kinases that modulate the activity of key cellular enzymes, proteins that control kinases, and transcription factors that determine the levels of gene expression. These components of signal transduction are themselves subject to intricately balanced controls in the normal cell. A disturbance of these controls can have profound consequences for the growth properties of the cell and can lead to oncogenic transformation.

Various Kinds of Genetic Change Activate the Tumorigenicity of Oncogenes

As cellular genes, oncogenes can become deregulated by several kinds of genetic change (Figure 2). Transduction by a retrovirus places the expression of the oncogene under the control of viral promoter and enhancer sequences and introduces mutations in the oncogene that change the inherent activity of the gene product. Retroviruses can also activate the tumorigenic potential of an oncogene by inserting their dominant promoter and enhancer sequences near the cellular

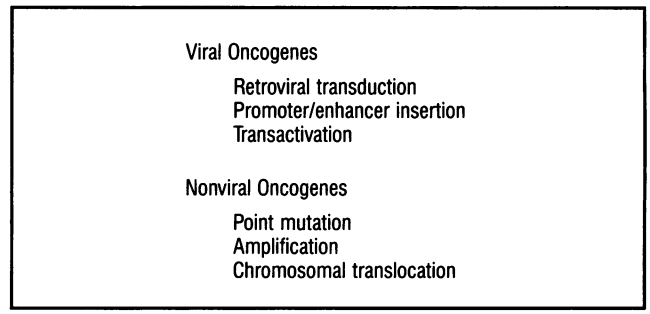

Figure 2.—The latent tumorigenicity of oncogenes can be activated by various kinds of genetic change. There are 3 retroviral mechanisms, of which transduction is the most efficient and promotor/enhancer insertion the most common. Transactivation may play an important part in the leukemia induced by the human T-cell leukemia virus, but final proof is still lacking. All 3 nonviral mechanisms have been found in human tumors.

oncogene and thereby increasing the expression of that gene. Some retroviruses, among them the human immunodeficiency virus and the human T-cell leukemia or lymphoma virus, may also increase the expression of cellular oncogenes by producing a transcription factor that alters gene expression when it interacts with specific gene regulatory sequences, including those of cellular oncogenes.

The latent oncogenicity of cellular oncogenes can also be activated by nonviral genetic changes. Mutations in the coding sequences of an oncogene can alter the response of the corresponding protein to regulatory molecules. Translocation of a cellular oncogene to another chromosome can bring the oncogene under the influence of strong cellular enhancer

regions that elevate its level of expression. Translocation can also activate the oncogenic potential of the oncogene by fusing it with another gene. Oncogenes can be amplified, and increased copy numbers of the gene per cell usually lead to increased amounts of the corresponding protein. All these mechanisms of deregulation have been found in tumors of animals and humans. The intervention of retroviruses is only one of several possible ways by which a cellular oncogene can become tumorigenic.

Human Tumors Harbor Activated Oncogenes

If DNA is extracted from human bladder carcinoma cells and introduced into normal mouse cells, the recipient cells undergo oncogenic transformation (Figure 3). The DNA responsible for this transformation has been identified as a mutated human version of the *ras* oncogene, a gene known from a tumor-producing murine retrovirus. The mutated human *ras* acts as a dominant transforming gene. Its product prevails over the regulated, cellular form of *ras*. Oncogenic mutations in *ras* are common in many human tumors, especially carcinomas of the colon, the urinary bladder, and lungs.

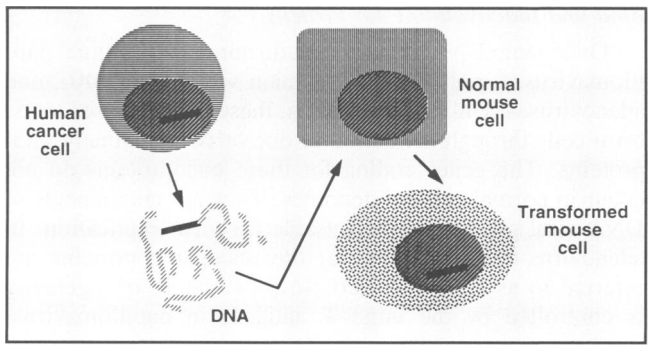

Figure 3.—DNA extracted from some human tumors or tumor cell lines contains genetic information that can transform a normal mouse cell into a tumor cell. That oncogenic information is often the activated form of the *ras* oncogene, a gene that is also transduced by retroviruses. Numerous other dominant oncogenes have been discovered by this gene transfer technique.

In malignant hematopoietic neoplasms, oncogenes are often activated by chromosomal translocation. The first such example was chronic myelogenous leukemia with its characteristic Philadelphia chromosome. In the Philadelphia chromosome, the *abl* oncogene of chromosome 9 is fused to the cellular gene *bcr* on chromosome 22. The result is a protein coded for jointly by *bcr* and *abl* sequences. The ABL protein, known for its leukemogenic potency in the mouse, is a protein kinase. The large BCR-ABL fusion product may also function as a deregulated protein kinase, but it contains additional structural features that suggest other possible growth-promoting activities. In Burkitt's lymphoma, the *myc* oncogene, known for its leukemogenic activity in chickens, mice, and cats, is translocated near an immunoglobulin enhancer and is expressed under the control of this enhancer. This deregulated expression of *myc* must be an important factor in lymphomagenesis because it is seen in all cases of Burkitt's lymphoma. Promyelocytic leukemia is characterized by a reciprocal translocation between chromosomes 15 and 17, resulting in gene fusions at both translocation points (Figure 4). One of these generates a product that consists of the retinoic acid receptor attached to sequences of the *pml* gene, which codes for a transcription factor. The PML–retinoic acid receptor chimera probably exerts highly aberrant transcriptional control. The remissions induced in promyelocytic leukemia by retinoic acid therapy are most likely related to the genetic rearrangement affecting the retinoic acid receptor.

Amplification of oncogenes can indicate advanced tumor development. In neuroblastoma a variant of the *myc* oncogene is amplified in the late stages of tumor development, and in mammary carcinoma the amplification of the *erb* B-2 oncogene, a relative of the epidermal growth factor-receptor gene, is correlated with the disseminated form of this malignant disorder.

The normal growth-regulatory function of cellular oncogenes, the proven tumor-inducing potential of their mutated versions, and the common occurrence of such mutated oncogenes in human tumors all are strong indications of a causal role for oncogenes in human cancer.

Oncogenes Cooperate to Induce Cancer

In some experimental systems, a single oncogene can induce the transformation of a normal cell to a tumor cell; the single gene is necessary and sufficient for the process of oncogenesis. Oncogenes that are transduced by retroviruses, in particular, show this high potency, possibly because they are both overexpressed and mutated structurally. Often, however, a single activated oncogene induces cellular changes that are only partly between normal and tumor cells. Enhanced growth properties may be observed without tumorigenicity. In these situations, two oncogenes with different biochemical functions may complement each other to achieve full transformation. For instance, the activated *ras*

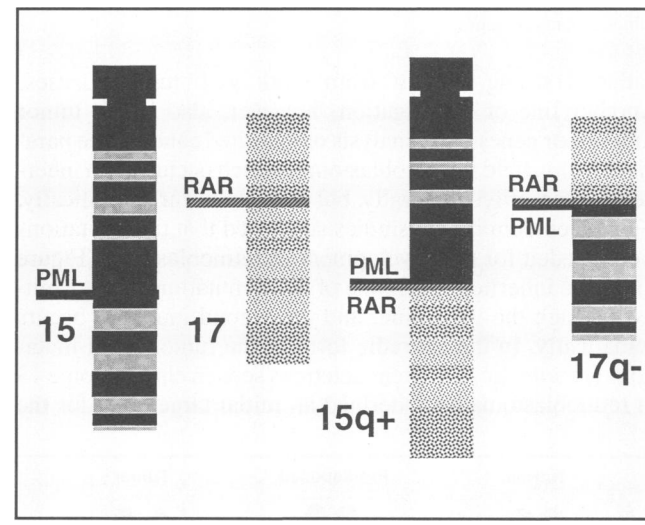

Figure 4.—The translocation between chromosomes 15 and 17 is characteristic of acute promyelocytic leukemia. It results in the fusion of the retinoic acid receptor to a transcription factor, PML. The fusion protein is probably a malfunctioning transcriptional regulator.

oncogene is a poor transformer for normal rat fibroblasts that are freshly explanted from the animal. In conjunction with an activated *myc* oncogene, however, *ras* becomes an efficient transformer. Several such combinations of complementing oncogenes exist, a reminder of the fact that carcinogenesis is a multistep process. In human tumors, too, more than one growth-regulatory gene is changed. The oncogenic phenotype of the cell results from the combination and cooperation of these multiple genetic changes.

Observations on Inherited Cancer Point to the Existence of Tumor Suppressor Genes

In an important experiment performed almost three decades ago, tumor cells were fused with normal cells to produce hybrids that contained the genetic material of both parental cell types. Surprisingly, in some combinations the hybrid cells were nontumorigenic but, on culture and following the loss of chromosomes from the normal parent, tumorigenic variants reappeared in the population (Figure 5). These observations can be explained by postulating the existence of genes in the normal genome that suppress the oncogenic phenotype. Loss of these tumor suppressors allows the reemergence of malignant cellular properties. Initially these experiments did not receive the attention they deserved, in part because they seemed incompatible with the concept of the dominant transforming oncogene, a concept that had

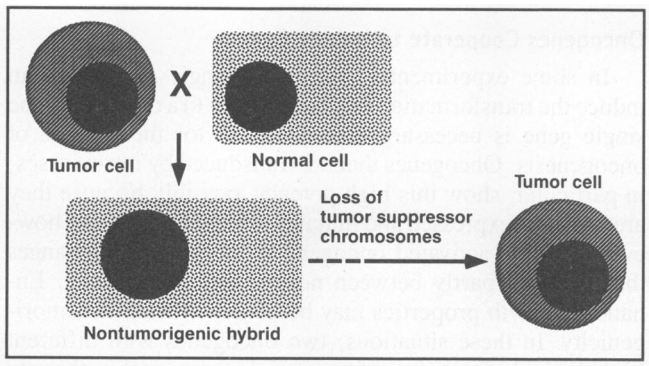

Figure 5.—Fusion of a tumor cell with a normal cell often yields a nontumorigenic hybrid. Loss of chomosomes from the normal parent leads to the reemergence of malignant properties. The lost chromosomes may therefore contain tumor suppressor genes.

gathered strong support from work with tumor viruses. Another line of investigation, however, also led to tumor suppressor genes—the analysis of inherited cancer. The paradigm in this field is retinoblastoma, which occurs as an inherited cancer, often bilaterally, but can also occur sporadically. Genetic epidemiologic studies suggested that two mutations were needed for the development of retinoblastoma (Figure 6). In the inherited form, one of these mutations is transmitted through the germ line, and the second mutation occurs somatically. In the sporadic form of the tumor, both mutations are somatic. Frequent deletions seen in chromosome 13 in retinoblastoma cells defined an initial target area for the

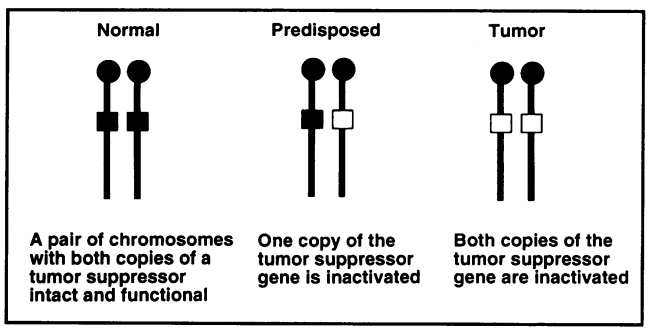

Figure 6.—Retinoblastoma results from two mutations that inactivate both alleles of the same gene, the Rb tumor suppressor. In the inherited form of this disease, one of the inactivating mutations is transmitted through the germ line and the second one occurs during somatic development. In the sporadic form, both Rb mutations are somatic.

study of the causal mutations and led to the discovery that both mutations affect the same gene, inactivating its function. In its active state, the retinoblastoma (Rb) gene codes for a tumor suppressor protein. When both copies of the gene are functionally lost, the resultant lack of growth-attenuating activity causes oncogenic transformation of cells in a specific state of differentiation, such as retinoblasts. The second mutation in the Rb gene can occur by somatic crossover, by nondisjunction followed by duplication of the mutated gene, or by gene conversion—all mechanisms that generate homozygosity in the Rb locus. This homozygosity or loss of heterozygosity of specific chromosomal loci in tumor tissue has become an important signal that marks the location of tumor suppressor genes, both copies of which must be inactivated to abolish the tumor-suppressive effect.

The Rb gene has been cloned. It codes for a protein that is localized in the cell nucleus. If Rb is introduced and overexpressed in tumor cells that lack a functional copy of that gene, the oncogenicity of these cells is substantially reduced or abolished, showing that Rb does have a tumor-suppressive effect in the cell.

Oncoproteins of DNA Tumor Viruses Bind and Inactivate the Rb Protein

Oncogenic DNA viruses include human and animal papillomaviruses, polyomavirus, simian virus 40 (SV40), and adenoviruses. Unlike retroviruses, these DNA viruses transform cells through the action of one or two genuinely viral proteins. The genes coding for these oncoproteins do not occur in normal cellular genomes. They are components of DNA viral genomes indispensable for virus replication. In adenovirus-transformed cells, the oncogenic proteins are referred to as E1A and E1B. In SV40 cells, oncogenicity is controlled by the large T antigen; in papillomavirus-

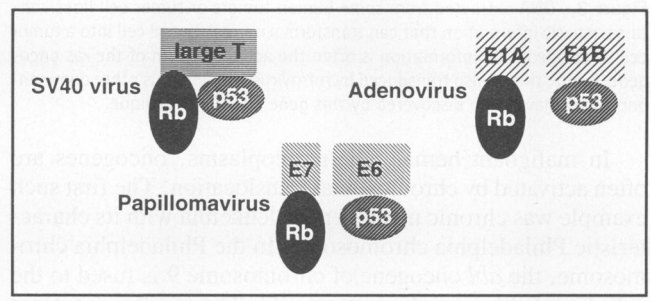

Figure 7.—Three types of DNA virus—simian virus 40 (SV40), adenovirus, and papillomavirus—code for proteins that induce the oncogenic transformation of the cell. These proteins bind to and inactivate the retinoblastoma (Rb) and p53 tumor suppressor proteins. The oncogenicity of these DNA viruses probably derives from this inactivation of Rb and p53.

transformed cells, the oncoproteins are E6 and E7 (Figure 7). Several of these oncoproteins—E1A, large T antigen, and E7—bind the Rb protein; others—E1B, large T antigen, and E6—also bind another cellular tumor suppressor protein, p53, which will be discussed later.

The Rb protein is itself regulated by phosphorylation that varies with the phase of the cell cycle. During the S phase, characterized by active DNA synthesis, the Rb protein is hyperphosphorylated. This highly phosphorylated form lacks the characteristic growth-attenuating properties of the underphosphorylated form that predominates during the quiescent G_1 phase. The oncoproteins of DNA tumor viruses

bind only the active, underphosphorylated form of the Rb protein. Binding to Rb protein takes place in the same regions of the oncoproteins that are needed for transformation. DNA tumor viruses may therefore transform normal cells into cancer cells by coding for proteins that bind and inactivate the tumor suppressor proteins Rb and p53.

Rb Regulates Gene Expression

The interactions of the Rb protein with DNA viral oncoproteins interfere with the physiologic functions of Rb. These functions involve protein-protein binding in normal cells. The active, underphosphorylated Rb protein binds the general transcription factor E2F, thereby inhibiting its activity. In a cell that is transformed by a DNA tumor virus, such as adenovirus, the E1A protein dissociates the union between Rb protein and E2F, allowing E2F to become active when its activity should be reduced by Rb. Thus, Rb controls gene expression through the transcription factor E2F. Interference with this transcriptional regulation can lead to oncogenic transformation of the cell.

Tumor Suppressor p53 Is Often Defective in Human Tumors

The tumor suppressor protein p53 is bound by oncoproteins of DNA tumor viruses. Genetic inactivation of p53 is usually caused by mutation rather than by deletion as in Rb. In cells that lack or have reduced p53 function and consequently are transformed, the normal phenotype can be largely restored by reintroducing and overexpressing a clone of normal p53. The protein is also a transcriptional regulator. It can activate transcription in experimental systems, but this may not be its only function. Mutated forms of p53 that have lost their tumor-suppressive effect no longer stimulate transcription. Mutations that inactivate p53 function are being found in an increasing number of human tumors. Carcinoma of the cervix is a particularly instructive example. Papillomaviruses play a causal role in the genesis of this tumor, and most tumors and tumor cell lines contain papillomaviral genetic material expressing the oncoproteins E6 and E7, which inactivate Rb and p53. Some tumors and tumor cell lines are free of papillomaviruses, however, and probably have a nonviral origin. In these tumors, p53 is genetically mutated and inactive, while in virus-induced tumors p53 is genetically wild type. The end result is the same in both cases: Normal p53 function is eliminated, either phenotypically through combining with a viral oncoprotein or genetically through a disabling mutation. The fact that two different oncogenic mechanisms generate a lesion affecting the function of the same tumor suppressor emphasizes the importance of the suppressor in the regulation of cell growth.

Gene Class	No.	Normal Role	Viral Carcinogenesis	Nonviral Carcinogenesis
Oncogenes	>60	Positive regulator	Carried or activated by retrovirus	Dominant mutations
Tumor suppressor genes	>>7	Negative regulator	Bound and inactivated by viral oncoproteins	Recessive mutations, both copies of the gene inactive in cancer

Figure 8.—Oncogenes and tumor suppressor genes are the yin and yang of growth control. Oncogenes become activated through a gain of function; tumor suppressor genes become oncogenic through a loss of function.

The importance of p53 is also illustrated by the Li-Fraumeni syndrome, a genetic susceptibility to cancer that is characterized by an extraordinarily high familial incidence of tumors at various sites. Carriers in families with the syndrome have an inactivating mutation affecting one copy of the p53 gene, and this mutation is transmitted to offspring through the germ line. The familial tumors show inactivation of p53.

Stage	Mutated Gene	Protein	Type of Regulator	Chromosome
1 *benign*	MCC APC	Transcription factors	Tumor suppressors	5 5
2	ras	Signal transducer	Oncogene	12
3	DCC	Cell adhesion molecule	Tumor suppressor	18
4 *malignant*	p53	Transcription factor	Tumor suppressor	17

Figure 9.—The genetic changes leading to tumorigenesis have been extensively studied in colon carcinoma. Several tumor suppressor genes are lost or inactivated, and at least 1 oncogene is activated.

Cell Malignancy Results From Many Changes in Oncogenes and Tumor Suppressor Genes

The actions of oncogenes and tumor suppressor genes are opposite and complementary (Figure 8). Oncogenes are positive and tumor suppressor genes are negative growth regulators. There are nearly 100 oncogenes known but fewer than 12 tumor suppressor genes. The number of the latter is, however, rapidly increasing. Oncogenes become tumor-inducing agents as a consequence of genetic changes that deregulate their physiologic activity. These changes are typically dominant—a single copy of an activated oncogene in the cell can transform. Normal copies of the oncogene are ineffective in counteracting the oncogenic change. Oncogenes can become activated through the intervention of a retrovirus or by nonviral mechanisms that alter expression levels or coding information. Tumor suppressor genes can exert a growth-regulating effect as single alleles. An oncogenic change usually involves the inactivation of both copies of the gene in the cell. Inactivation of just one copy is a recessive change but can increase the probability of an identical change in the second copy of the gene. Viral interference with the function of tumor suppressor genes occurs at the level of the protein, not the gene. DNA tumor virus oncoproteins bind to and inactivate tumor suppressor proteins. Oncogenes become tumorigenic through a gain of function; tumor suppressor genes acquire oncogenicity through the loss of function.

An instructive example for multiple genetic changes in carcinogenesis is carcinoma of the colon (Figure 9). The development of this tumor proceeds through stages of increasing malignancy starting with benign adenoma and ending with aggressively invasive carcinoma. The acquisition of more and more malignant behavior is accompanied by an accumulation of mutations affecting oncogenes and tumor

suppressor genes. The sequence of these mutations is not fixed; the important feature is the accumulation of multiple genetic changes, each contributing incrementally to the loss of growth control.

Molecular Genetics of Cancer Originated From the Work of Boveri and Rous

Two ideas have dominated the course of cancer research in this century: the idea that cancer results from a genetic change and therefore a cancer cell differs genetically from its normal counterpart, and the idea that viruses can be oncogenic in animals and humans, revealing key mechanisms of oncogenesis. These ideas can be traced back to two seminal figures, Theodor Boveri (1860-1916) and Peyton Rous (1879-1970). Although Rous was Boveri's junior by almost a generation, both did their most important work in the first decade of this century.

Boveri was a professor at the University of Würzburg, Germany. He made fundamental discoveries in chromosome structure and function and in animal development. In a startlingly prescient synthesis of what was then known about genetics and cancer, he proposed in 1902 that cancer was due to chromosomal (genetic) changes. He published his ideas in 1914 in a small volume entitled *Zur Frage der Entstehung maligner Tumoren* (*The Origin of Malignant Tumors*). Today his hypothesis is supported by abundant evidence and provides the theoretical underpinning of virtually all cancer research.

Although Rous did not favor somatic mutation as the basis for cancer, in 1911 he discovered the first oncogenic retrovirus, RSV, one of the most effective somatic mutagens known. Rous was affiliated with the Rockefeller Institute in New York City throughout his scientific career. His pioneering work also extended to DNA tumor viruses, specifically the papillomaviruses. The legacy of Rous therefore includes both oncogenes, revealed by retroviruses, and tumor suppressors, the targets of DNA tumor viruses. He was awarded the Nobel Prize in physiology and medicine in 1966.

By identifying growth-regulatory genes that are altered in cancer, molecular genetics has marked targets for a specific and effective therapy. The recent observation that returning a single tumor suppressor to normal function can abolish the tumorigenicity of a cell with multiple genetic defects is an encouraging sign. The time has come to work on a gene-targeted therapy for cancer.

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